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HEMOCOMPATIBLE COATINGS ON HYDROPHOBIC POROUS POLYMERS

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BACKGROUND

Field of the Invention

The present invention relates to the field of hemocompatible coatings on hydrophobic porous polymeric materials and, in particular, to hemocompatible coatings based upon complexes of heparin deposited upon porous hydrophobic polymers, typically expanded PTFE.

Description of Related Art

Continuing advances in medical technology have led to the development and use of numerous medical devices that come into contact with blood or other bodily fluids. To be concrete in our discussion, we focus herein on the particular example of medical devices coming into contact with mammalian blood, particularly human blood, not intending thereby to limit the scope of the present invention to medical devices used exclusively on human patients. In using such devices, it is important that contact of the blood or other bodily fluid with the various components of the medical device not cause therapeutically detrimental alterations to the fluid. In many cases, it is desirable to coat such devices with materials to enhance the biocompatiblity of the devices, including coatings that contain bioactive agents, anticoagulants, antimicrobial agents or a variety of other drugs.

It is convenient to consider blood-contacting medical devices as invasive or extra-corporal, although some devices span both classes. Invasive devices are used internally in the treatment of the patient, implanted into the patient for an indefinite or extended period of time or inserted into the patient for relatively brief periods. In many cases, the materials comprising the blood-contacting portions of the invasive device lack sufficient biocompatibility and/or hemocompatibility, tending to cause changes harmful to the patient in the blood or other fluid coming into contact with the surface (or surfaces) of the device. In such cases it is desirable to coat the surfaces of these devices with materials to enhance the biocompatiblity and/or hemocompatibility. Invasive devices that are typically coated with biocompatible or therapeutic substances include implantable artificial orthopedic devices, dental implants, intravascular catheters, emboli capturing systems, epicardial immobilization devices, grafts, stents, intraluminal prosthetic devices and artificial heart valves, among others.

There are also many examples of extra-corporal medical devices that come into contact with blood in which blood is transported and/or processed external to the patient. A few representative examples include cardiopulmonary bypass devices, kidney dialysis equipment, blood oxygenators, separators and defoaming devices, among others. Following such extra-corporal processing, the blood or other bodily fluid may be reintroduced into the patient, transported for storage and/or for introduction into another patient. In using such extra-corporal devices, it is important that contact of the blood or other bodily fluid with the various components of the device not cause therapeutically detrimental alterations to the fluid.

It is important in some cases that the surface or the surfaces of the invasive or extra-corporal medical device be coated with substances having therapeutic

functions, wherein the coatings may serve several functions in addition to increasing the biocompatibility/hemocompatibility of the surface. Examples of such additional functions include the release of one or more therapeutic agents into the blood in appropriate dosages with appropriate timed-released characteristics and at the proper location within the patient. Thus, the medical device may serve as a convenient delivery platform for the delivery of therapeutically beneficial drugs in addition to its other functions.

One important application related to implantable devices arises in connection with endoluminal stents, particularly as occurring in connection with percutaneous transluminal angioplasty ("PCTA"). Following balloon angioplasty, the lumen of the just-expanded vessel may contract due to several causes. An initial rebound of the walls of the vessel may occur following removal of the balloon. Further thrombosis or restenosis of the blood vessel may occur over time following the angioplasty procedure. The result is often the necessity for another angioplasty procedure or surgical by-pass. Endoluminal stents have been in use for several years in conjunction with a surgical procedure inserting a tube or stent into the vessel following the PCTA procedure to assist in retaining the desired intraluminal opening. A review of the procedure may be found in Endoluminal Stenting by Ulrich Sigwart, Ed. (W. B. Saunders, 1996). A compendium of coronary stents is given in Handbook of Coronary Stents, 3rd Ed. by P. W. Serruys and M. JB Kutryk, Eds. (Martin Dunitz Ltd., 2000). However, even with stenting, occlusions frequently recur within the stent requiring further PCTA or by-pass surgery. Such restenosis following PCTA and the insertion of a stent is sought to be prevented by the use of coated stents. Coatings on stents are often used for the delivery of anticoagulants or other medication that assist in preventing thrombosis and restenosis.

Heparin is an anticoagulant drug composed of a highly sulfated polysaccharide, the principle constituent of which is a glycosaminoglycan. In combination with a protein cofactor, heparin acts as an antithrobin (among other medical effects as described, for example, in Heparin-Binding Proteins, by H. E. Conrad (Academic Press, 1998)). Heparin is an attractive additive to coat on the surface(s) of blood-contacting devices in order to increase the hemocompatibility of the material and/or to release heparin or heparin complexes into the blood to combat thrombosis and restenosis.

The heparin molecule contains numerous hydrophilic groups including hydroxyl, carboxyl, sulfate and sulfamino making underivatized heparin difficult to coat onto hydrophobic polymers. Thus, many types of complexes of heparin with hydrophobic counter ions have been used in order to increase the ability of the heparin-counter ion complex to bind to hydrophobic surfaces. Such counter ions are typically cationic to facilitate binding with anionic heparin, and contain a hydrophobic region to facilitate bonding with the hydrophobic polymer. Typical heparin complexes include, but are not limited to, heparin complex with typically large quaternary ammonium species such as benzylalkonium groups (typically introduced in the form of benzylalkonium chloride), tridodecylmethylammonium chloride ("TDMEC"), and the commercial heparin complex offered by Baxter International under the tradename DURAFLO or DURAFLO II. Herein we denote as "heparin complex" any complex of heparin with a hydrophobic counter ion, typically a relatively large counter ion. Examples of heparin complexes are described in the following U. S. Patents (incorporated herein by reference): 4,654,327; 4,871,357; 5,047,020; 5,069,899; 5,525,348; 5,541,167 and references cited therein.

Considerable work has been done in developing coatings for application to various medical devices in which the coatings contain at least one form of heparin

or heparin complex. Combinations of heparin and heparin complexes with other drugs, as well as various techniques for tailoring the coating to provide desired drug-release characteristics have been studied. Examples of such work include that of Chen *et. al.* (incorporated herein by reference), published in J. Vascular Surgery, Vol 22, No. 3 pp. 237-247 (September 1995) and the following U. S. Patents (incorporated herein by reference): 4,118,485; 4,678,468; 4,745,105; 4,745,107; 4,895,566; 5,013,717; 5,061,738; 5,135,516; 5,322,659; 5,383,927; 5,417,969; 5,441,759; 5,865,814; 5,876,433; 5,879,697; 5,993,890 as well as references cited in the foregoing patents and article.

Implantable medical devices often require some degree of porosity to enable blood to come into contact with underlying tissues, to increase the surface area for delivery of therapeutic substances, or for other purposes. Therefore, porous polymers are widely used in medical devices. The advantages of porosity are not limited to implantable devices, and porous materials are used in extra-corporal devices as well as invasive medical devices. However, the problem of coating with heparin is exacerbated if the hydrophobic polymer is also porous. In addition to binding with the hydrophobic surface, the heparin complex must also penetrate into the interstices of the porous structure of the polymer and bind to all or substantially all of the polymer surface that comes into contact with blood.

Fluorinated polymers are typically chemically unreactive, have low surface energy and are hydrophobic. Such properties are generally favorable for use in medical devices as described, for example by F. H. Silver and D. L. Christiansen in Biomaterials Science and Biocompatibility, (Springer-Verlag, 1999) p. 19. Poly(tetrafluoroethylene), PTFE, is a polymeric material with repeating units of $(-CF_2CF_2-)$ having numerous commercial uses, including in blood-contacting devices, due in large part to its chemical inertness and desirable physical

properties. PTFE in the form of a film or solid has low surface energy and, therefore, is a relatively difficult surface to coat (or "wet"). "Wetting" typically indicates the tendency of a liquid to spread and coat the surface onto which it is placed. The specific relationship between surface energy and the contact angle at the interface between a drop and the surface (the "wetting") is given in standard references including Physical Chemistry of Surfaces 6th Ed. by A. W. Adams and A. P. Gast (John Wiley, 1997), p. 465 ff. A contact angle between the liquid and the surface greater than approximately 90^0 typically indicates a non-wetting liquid on that particular surface.

In many medical and non-medical commercial uses, it is desirable to have PTFE in the form of a porous film that retains adequate physical strength for the particular application while not substantially increasing the cost of the material. Expanded PTFE (hereinafter "ePTFE") is a form of PTFE that has been physically expanded along one or more directions to create a porous form of PTFE having varying amounts of porosity depending on several factors including the specific procedures for performing the mechanical expansion. The porous ePTFE thus created is useful for the manufacture of several commercial products as illustrated (for example) by the work of Gore in U. S. Patents 3,953,566 and 4,187,390 and the work of House *et. al.* in U. S. Patent 6,048,484. Applications to stents include the work of Lewis *et. al.* (U. S. Patent 5,993,489) and Bley *et. al.* (U. S. Patents 5,674,241 and 5,968,070). The chemical inactivity, and other properties of fluorinated polymers including PTFE and ePTFE, have made them attractive substances for use in many medical and blood-contacting devices. Representative examples include dental implant devices (Scantlebury *et. al.* U. S. Patent 4,531,916), grafts, stents and intraluminal prosthetic devices (Bley *et. al.* 5,674,241 and 5,968,070; Goldfarb *et. al.* 5,955,016; Lewis *et. al.* 5,993,489; Tu *et. al.* 6,090,134).

Expanded PTFE is widely used in medical devices and is perhaps one of the most widely used vascular graft materials. In fact, ePTFE has a large range of application in blood-contacting medical devices including, but not limited to, segmental venous replacements, reconstructed veins in organ transplantation, polymer catheters, in-dwelling catheters, urological and coronary stents, covered stents, heart valves, dental implants, orthopedic devices, vascular grafts, synthetic by-pass grafts and other invasive and implantable medical devices. In addition, ePTFE can be used in extra-corporal blood-contacting devices. Examples include, but are not limited to, heart by-pass devices, kidney dialysis equipment, blood oxygenators, defoaming machines, among others.

Figure 1 is a scanning electron micrograph of porous ePTFE from the work of House *et. al.* (U. S. Patent 6,048,484). Figures 2A and 2B are schematic depictions of two forms of ePTFE showing biaxially oriented fibrils (Fig. 2A), and multiaxially oriented fibrils (Fig. 2B). Both Fig. 2A and 2B are from House *et. al. (supra).* Low surface energy characteristic of fluoropolymers and other hydrophobic polymers, in combination with the porosity of ePTFE, make the application of a coating to ePTFE, including coating of the interior surfaces of the pores, a significant challenge. Providing such a coating for ePTFE is one objective of the present invention.

However, when used in a blood-contacting environment, ePTFE tends to be thrombogenic and its porosity may release entrapped gases (which may itself be a source of throbogenicity as discussed, for example, by Vann *et. al.* U. S. Patent 5,181,903). Therefore, considerable effort has gone into the coating of ePTFE to reduce its throbogenicity and/or provide other therapeutic effects. Hemocompatibility can be achieved by a variety of means, including coating with a hydrophilic, biologically passive, polymer, or by coating with materials having a biologically active component such as heparin or a complex of heparin including

the commercially available heparin complex DURAFLO or DURAFLO II (Baxter Healthcare, Inc.). Improved procedures for coating ePTFE with hemocompatible substances, typically substances containing derivatives or complexes of heparin, and the improved hemocompatible materials so produced are among the objects of the present invention. We use the expressions "derivative of heparin" and "complex of heparin" interchangeably herein without distinction to indicate a chemical combination of heparin with a counter ion.

Although fluoropolymers have been among the most commonly used materials for blood-contacting devices, polyurethanes, polyethylene terephthalates ("PETs") and numerous other fluorinated and non-fluorinated polymers have also found considerable application. Modifications of polyurethanes, PETs and other plastics have included the introduction of coatings for antithrombogenic and anticoagulant properties. PET is an example of a non-fluorinated polymer that is highly hydrophobic and therefore difficult to coat with polar, aqueous materials such as heparin. PTFE is but one example of the general chemical class of fluoropolymer. that also includes FEP (fluorinated ethylene propylene), PFA (perfluoroalkyl vinyl ether and tetrafluoroethylene co-polymer), PVDF (polyvinylidenedifluoride), PVF (polyvinylfluoride), PCTFE (polychlorotrifluoroethylene), ETFE (ethylene and tetrafluoroethylene co-polymer) TFB (terpolymer of vinylidenedifluoride, hexafluoropropylene and tetrafluoroethylene) and other fluoropolymers as known in the art and described in many references including, for example, W. Woebcken in Saechtling International Plastics Handbook for the Technologist, Engineer and User, 3rd Ed., (Hanser Publishers, 1995) pp. 234-240, incorporated herein by reference.

Coating the interior regions of highly porous materials such as ePTFE with significant amounts of a hemocompatible coatings presents special challenges in addition to the hydrophobicity, deriving in part from the relative inaccessibility of much of the surface to be coated.

SUMMARY

The present invention relates to methods of coating porous, hydrophobic polymers with a hemocompatible coating, to the materials produced thereby and to medical devices in which at least a portion of the blood-contacting surfaces thereof comprise such hemocompatible materials. One embodiment of the present invention relates to the coating of expanded poly(tetrafluoroethylene), ePTFE, with one or more complexes containing heparin bonded to a hydrophobic counter ion. The porous nature of ePTFE makes penetration and coating of the interior regions of the material difficult due to surface tension effects, entrapped gases and similar phenomena characteristic of liquid penetration into porous structures. Such porosity-related challenges to coating are exacerbated by the low surface energy of PTFE. The present invention makes use of a solvent that both penetrates the porous regions of ePTFE and dissolves heparin complexes. Solvents used pursuant to the present invention include non-polar solvents that wet PTFE.

A hemocompatible coating is dissolved in a mixture of solvents in which a first solvent wets the polymer to be coated and the second solvent enhances the solubility of the hemocompatible coating material in the solvent mixture. First solvents that have the property of wetting hydrophobic polymers are typically non-polar. Typical second solvents include polar solvents such as organic alcohols, ketones, among other possibilities. In one embodiment, azeotropic mixtures of the second solvent in the first solvent are used, although concentrations of the second solvent from near zero up to saturation may be used. The present invention also relates to medical devices, including endoluminal stents, that employ the coated materials of the present invention. Producing a porous material having a hemocompatible coating on at least some blood-contacting surfaces thereof is a primary object of the present invention. Medical devices using such materials in a blood-contacting environment have the advantages of reducing the accumulation platelets and thrombus on the coated surfaces.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Scanning electron micrograph of ePTFE from U. S. Patent 6,048,484.

Figure 2A: Schematic depiction of porous structure of ePTFE from U. S. Patent 6,048,484 depicting biaxially oriented fibrils.

Figure 2B: Schematic depiction of porous structure of ePTFE from U. S. Patent 6,048,484 depicting multiaxially oriented fibrils.

Figure 3: Cut-away depiction of a portion of a covered stent.

DETAILED DESCRIPTION

The present invention relates to the coating of porous, hydrophobic polymers, typically fluoropolymers such as expanded poly(tetrafluoroethylene), ePTFE, with hemocompatible coatings, so as to perfuse and coat substantially all regions of the surface that come into contact with blood, including the interior regions of the porous structure that are difficult to access and difficult to coat by conventional means. Complexes of heparin are the typical hemocompatible coatings employed in some embodiments of the present invention.

We follow the conventional usage that "wetting" indicates that the contact angle formed by the tangent to the surface of the liquid and the surface of the solid at the point of contact is less than 90^0 (measured through the liquid phase) such that the liquid tends to spread over the surface of the solid. Conversely, nonwetting indicates that the liquid tends to ball up on the surface of the solid and run off the surface easily. Contact angles are known in the art and provide one criteria by which candidate solvents of the present invention can be identified. For example,

contact angles of selected liquids with selected surfaces (including fluoropolymers such as PTFE, FEP) are provided in Physical Chemistry of Surfaces 6th Ed. *(supra)* pp. 365-366.

The present invention is not inherently limited to ePTFE or to fluoropolymers as a class. Porous hydrophobic polymeric materials, that are typically difficult to coat with hemocompatible materials by procedures of the prior art are included within the scope of the present invention. Examples of porous hydrophobic polymers include the following: porous polyethylene, porous polypropylene, porous polyurethanes, porous polyacrylates, porous polymethacrylates, among others. Biocompatible polyurethanes, PETs and other polymers have also been used as blood-contacting substances in medical devices, subject to coating with heparin complexes and/or other hemocompatible or therapeutic molecules pursuant to the methods of the present invention. However, PTFE is but one example of a class of commercially important fluoropolymers. Other examples include those noted above; FEP, PFA, PVDF, PVF, PCTFE, ETFE, TFB and other fluoropolymers as known in the art. Blends containing ePTFE, other fluoropolymers and/or other hydrophobic polymers are included within the scope of the present invention. Such blends are coatable by means of the procedures described herein and the resulting coated materials useful in blood-contacting medical devices.

To be concrete in our discussions we describe in detail the particular embodiments in which expanded PTFE is coated with a hemocompatible coating containing heparin as one component thereof. Other embodiments making use of other porous hydrophobic polymers and/or other hemocompatible coatings consistent with the procedures and conditions of the present invention represent obvious modifications of the present invention and are included within its scope.

The present invention relates to coating ePTFE without distinction as to the particular microstructure present in the ePTFE prior to coating. Herein we use "ePTFE" to indicate any porous structure of the PTFE polymer, irrespective of its

specific and detailed microstructure and irrespective of the detailed procedure for its formation. Commercially available embodiments of ePTFE such as GORE-TEX (W. L. Gore and Associates) are included. In some embodiments of the present invention, mechanically expansion of PTFE is the means by which porosity is obtained. However, as described by Gore (U. S. Patents 3,953,566 and 4,187,390, incorporated herein by reference), mechanical expansion is not the only way to obtain porous PTFE. The coating procedures of the present invention can be used for coating porous polymeric materials, including ePTFE, irrespective of the specific mechanism by which the porosity is introduced into the material. However, for economy of language, we use "ePTFE" to denote a porous form of PTFE, however produced, recognizing that mechanically expanded PTFE is but one means of obtaining the desired porosity.

Liquids having contact angles with PTFE less than 90^0 include non-polar organic solvents such as alkanes (pentane, hexane, heptane and octane, among others) and cycloalkanes, freons or related materials such as chlorofluorocarbons ("CFCs") and hydrochlorofluorocarbons ("HCFCs"). Commercial solvents include CFCs and HCFCs such as "Techspray AMS Flux Remover" (from Techspray, Inc., of Amarillo, Texas) and "Gensolv 2004" (from Micro Care Corp. of Bristol, CT). Various ethers, tetrahydrofuran, dioxane are among the solvents wetting PTFE. For some embodiments of the present invention, a candidate solvent is any solvent that is known to wet fluoropolymers (particularly ePTFE) or the hydrophobic polymer of interest. Although pure solvents are discussed herein, this is merely for economy of language. Mixtures of solvents that retain the property of being able to wet the hydrophobic surface, particularly ePTFE, are included within the scope of the present invention.

A hydrophobic complex of heparin is dissolved in the polymer-wetting primary solvent for penetration into the porous structure and deposition onto ePTFE in some embodiments of the present invention. Some (typically small) amount of heparin complex dissolves in pure polymer-wetting solvent as described above, but typically does not lead to biologically useful amounts of heparin being

deposited onto the hydrophobic surfaces. Therefore, in some embodiments of the present invention, the solubility of heparin complexes is enhanced by the addition of relatively small amounts of a polar solvent to the non-polar primary solvent. The non-polar primary solvent is chosen to provide adequate penetration into the interior of the porous hydrophobic material, while the polar solubility-enhancing component of the solvent is selected to facilitate dissolution of heparin complexes in the solvent mixture. Candidate polar solubility-enhancing additives included organic alcohols (methanol, ethanol, among others), ketones (acetone, methylethylketone, among others). Mixtures of one or more chemical compounds can also be used as the solubility-enhancing solvent.

It is desirable, but not inherently necessary in some embodiments of the present invention, that the polar solvent be added to the non-polar solvent in an amount so as to form an azeotropic mixture. Azeotropic mixtures have the property of evaporating such that the unevaporated liquid retains the same composition to dryness. In contrast, non-azeotropic mixtures typically become more concentrated in the less volatile solvent as evaporation proceeds. A solute will thus experience a changing solvent composition during evaporation for non-azeotropic mixtures. This may lead to precipitation of the solute and tend to create non-uniform coatings. Thus, while non-azeotropic mixtures may be used with acceptable results, azeotropic mixtures typically give better coatings.

One example of a substantially azeotropic mixture described in detail below includes a polymer-wetting solvent HCFC-225 containing about 6% methanol (by volume). This solvent mixture is found to be adequate in the some embodiments of the present invention. "HCFC-225" is a mixture of isomers of dichloropentafluoropropane, typically HCFC-225ca is $CF_3CF_2CHCl_2$ and HCFC-225cb is $CClF_2CF_2CHFCl$. However, azeotropic mixtures are not necessary in the present invention and adequate results are obtained with concentrations of polar solvent from approximately 0.00001% up to saturation of the polar solvent dissolved in the non-polar solvent. In some embodiments of the present invention, concentrations of polar solvent in the range from about 0.1% to about 10% by

volume are used. However, while the above ranges give therapeutically useful amounts of hemocompatible coatings, better quality coatings are typically obtained with concentrations in the range from approximately 0.1% to approximately 2%. A range from approximately 0.5% to approximately 1% is particularly useful in that 0.5% has enough hemocompatible material for therapeutically effective coatings by 1% is dilute enough to avoid webbing.

Thus, the present invention includes adding relatively small amounts of an organic alcohol (such as ethanol, methanol, among others) or a similar solubility-enhancing polar solvent to a polymer-wetting solvent. The solubility enhancing solvent is added to the polymer-wetting solvent in such quantity (typically small) that the mixed solvent provides adequate solubility for heparin complexes without substantially hindering penetration of the pores or wetting of the hydrophobic polymer. Thus, in one embodiment a mixed solvent is created that both wets ePTFE and delivers heparin to all surfaces of the porous structure.

Having dissolved a suitable heparin complex in a mixed solvent as described herein, coating of the ePTFE with the heparin complex may be performed by any convenient method that brings the heparin-containing solution into intimate contact with all surface regions of the ePTFE substrate including the interior regions of the pores. Dip coating is one technique that can be used in some embodiments of the present invention although other coating techniques known in the art may also be used, including spraying.

Figure 3 depicts a portion of an endoluminal stent in cut-away view, showing the interior region of the stent, 1, the struts, 2, and a covering, 3. The covering material for the stent, 3, is typically porous to allow blood flowing on the interior of the stent, 1, to come into contact with the interior surfaces of the lumen in which the stent is placed. Porous materials containing hemocompatible coatings thereon may be used in many medical devices, one example of which is stent covering, 3. Expanded PTFE is a typical stent covering material. Other materials for covering stents are described elsewhere herein and in the references cited.

Hemocompatible coatings placed onto stent cover, 3, include heparin and heparin complexes. One embodiment of the present invention relates to coating a ePTFE stent covering material with a heparin complex, typically DURAFLO or DURAFLO II. Typical pore sizes of ePTFE are in the range of approximately 5 μm (microns) to approximately 200 μm, commonly in the range from approximately 40 μm to approximately 120 μm.

EXAMPLES

DURAFLO II may be used herein in place of DURAFLO without modification.

1) Prepare a solution consisting of the hydrochlorofluorocarbon HCFC-225 and 6% by volume methanol whereby the methanol enhances the solubility of the heparin complex in the HCFC solvent.

2) Dissolve in the solution of step 1, a heparin complex, DURAFLO. The concentration of DURAFLO in the solution is selected to provide the desired coating of DURAFLO on the stent cover. Too little drug on the stent cover may be therapeutically ineffective. Too much may cause excess amounts of drug to be released into the blood soon after the stent is implanted, to the detriment of the patient.

3) Dip ePTFE into the solution of step 2 allowing the solution to perfuse throughout the ePTFE porosity and deposit the DURAFLO throughout.

4) Repeat step 3 if additional coating of DURAFLO is desired.

Other solvents that may be used in step 1 above include the following:

1-a) Techspray AMS Flux Remover containing approximately 6% methanol.

1-b) Genesolv 2004, dichlorofluoroethane containing approximately 4% methanol.

1-c) Cyclohexane including approximately 5% n-propanol.

Other solutes that may be used in step 2 above include the following:

2-a) TDMEC heparin.

2-b) Benzalkonium heparin.

Concentrations of solute in solvent may be any convenient value leading to the appropriate deposition of hemocompatible substance onto the surface of the polymer. Typical concentrations in the range of approximately 1% - 3% are found to give adequate coatings.

The material produced by the above procedure is a suitable stent covering material containing DURAFLO (or other heparin complex) coated on substantially all surfaces thereof that will be exposed to blood during use. Dip or spray coating is conveniently done on a porous, hydrophobic polymer already mounted on the struts, forming thereby a stent covering. However, the hydrophobic, porous material may be coated pursuant to the present invention before, during or following the fabrication of the material into a medical device. The timing of coating and device fabrication is determined in part by manufacturing considerations including the damage likely to result to the hemocompatible coating by processing during device fabrication.

The properties of the coating can be tested *in vitro* by standard testing methods including AT-III binding or anti-Factor Xa Assay. Other biological assays include various *ex vivo* shunts.

Having described the invention in detail, those skilled in the art will appreciate that, given the present disclosure, modifications may be made to the invention without departing from the spirit of the inventive concept described

herein. Therefore, it is not intended that the scope of the invention be limited to the specific embodiments illustrated and described.